

## Ethical concerns in the age of an advanced psychopharmacology

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### Introduction

Controlling, modulating or influencing mental activity, thoughts, beliefs and even human behavior has been an everlasting challenge in medicine and psychology. The nature and the environment have granted humanity different options to try to regulate sleep and wake. As demonstrated by history, *Papaver somniferum* and wine have had their say on sleep induction since antiquity (1).

Overcoming grief, stress and anxiety have also been among the targets, especially for traumatized persons. *Nepenthe* was the Homeric anti-sorrow drug, obviously not related to the panoply of antidepressants that are so widely used in the modern times (2).

The unending debate on mind-soul duality has had obvious philosophical implications but contributed very little to treatment of psychiatric patients (3, 4). Before the advent of antipsychotics, controlling agitated patients without the use of (maybe) inhuman mechanical contention was hardly achievable, although many attempts were made to do so (5, 6).

### Chance Discoveries

Antipsychotics and antidepressants were serendipitous discoveries, as they were both initially the byproducts of active principles that were synthesized and tried for other medical conditions. Their discovery was the result of previous, extensive research in chemistry that dated back to the nineteenth century. In an exhaustive review, López-Muñoz et al. offered plenty of historical details regarding the synthesis of the first antipsychotic: chlorpromazine (7).

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Received: 20 Dec 2021

Accepted: 28 Dec 2021

Published: 30 Dec 2021

#### Citation to this article:

Vyshka G, Ulqinaku D, Mana T. Ethical concerns in the age of an advanced psychopharmacology. *J Med Ethics Hist Med.* 2021; 14: 29.

According to some sources, this medication is the same as the *Laborit drug*, named in honor of the French doctor who led a team of researchers looking for an anti-shock cocktail in the field of anesthesia (8).

The discovery of chlorpromazine was in fact everything but mere chance, since related advancements in chemistry and continuous research had been ongoing for decades. Working on aniline and coal dyes, as well as their byproducts, scientists were able to synthesize phenothiazines (7). While studying the antimalarial effects of methylene blue and adding amino-alkylate chains to the phenothiazine ring, derivative compounds with antihistaminic properties were discovered that soon found their way into psychiatry. The ‘*magic bullet*’, a concept developed by Paul Ehrlich (1907) while working on trypan red as a valid treatment for syphilis, some years later became the ‘*effet dédésintéressement*’ (effect of disinterest) of Henry Laborit (1951), the French military physician. Together with his collaborators (Huguenard and Quarti) and other psychiatrists (Delay and Deniker), Laborit witnessed how calm, disinterested, quiet and collaborative psychiatric patients became as a result of taking chlorpromazine (9, 10). Many of them were catatonics and had even refused to eat until a few days before taking the medicine for the first time (11).

However, chlorpromazine was obviously not the only psychiatric drug discovered by chance: the anti-maniacal effects of lithium and the anti-depressant effects of isoniazid had a similar story. In the early 1950s Kline, Loomer and Saunders highlighted the

efficacy of iproniazid (an antitubercular drug) as an antidepressant and ‘energizer’ even among patients not suffering from tuberculosis (12, 13). Imipramine, a tricyclic antidepressant, was likewise a serendipitous discovery (13).

The effect of lithium as a mood stabilizer has had the same trajectory of discovery. A neurologist from Philadelphia (S.W. Mitchell) appraised the anticonvulsant and hypnotic properties of lithium as early as 1870 (14). However, John Cade re-discovered some psychotropic properties of the element in Melbourne (1949) while reporting the sedative but non-hypnotic effects of lithium salts in mania patients (15).

Since the number of chance discoveries in the field of psychopharmacology is considerable, dedicated authors have concentrated even on specifying what to call as purely “*serendipitous*” as opposed to what seems to be so. Thus, López-Muñoz et al. classified four patterns of this phenomenon (16):

- ❖ Pure serendipitous discoveries (for example, valproate sodium)
- ❖ Serendipitous observation leading to non-serendipitous discoveries (imipramine)
- ❖ Non-serendipitous discoveries secondarily associated with serendipitous observation (barbiturates)
- ❖ Non-serendipitous discoveries (haloperidol).

Beyond all doubts, apart from the dedication and passion in the work of renowned chemistry and pharmacology researchers, the discovery and the ensuing wide use of psychoactive drugs have enjoyed the spirit of

change – the so-called *Zeitgeist* – and have been supported by culture and the positive approach of the public at that specific period of time (17).

### ***Ethical Issues: Competence and Beyond***

Psychotropic drugs are not without side effects. However, this is not and must not be a deterrent against their use, as the risk/benefit ratio is clearly favorable. Turning an otherwise aggressive and confused patient into a sociable individual, calming him/her down, encapsulating if not wiping out delusions, liberating people from hallucinations and distorted reality perceptions are some of the good that these drugs can do, and have done.

Nevertheless, with litigation trends increasing in the field of medical treatment (fortunately much less in psychiatry than other specialties), and with antipsychiatry as a half-philosophical movement always at the corner, there can never be enough prudence and caution (18, 19). The dilemmas and debates are serious enough to lead to the coinage of the term *postpsychiatry*: apparently, closing an era and heading nowhere (20).

One of the major ethical issues related especially to the use of antipsychotics pertains to settings particular to certain individuals, above all prisoners, anti-regime advocates and political adversaries. Especially notorious is the abuse of these drugs in Eastern European countries, as well as the coining of particular forms of mental disease to stigmatize and discriminate

issenters (21). The Russian concept of schizophrenia and the sluggish form of it – widely unclear and not accepted – was the tip of an iceberg (22). Much more dangerous and crueler were of course the atrocious experiments on humans inside Nazi German concentration camps (23).

The fact is that for reasons beyond politics and extra-medical abuse, psychoactive drugs need special monitoring and their side effects are serious and have long-term implications. Severe adverse effects include: tardive dyskinesia, neutropenia, iatrogenic parkinsonism, cardiac arrhythmias, malignant hyperthermia, impotence, and amenorrhea resulting from the use of antipsychotics, and the very much debated issue of increased suicide rate related to the use of new-generation antidepressants. Furthermore, vulnerable groups such as patients of minor age, octogenarians and pregnant women will need extra monitoring (24), which is unfortunately not always feasible.

Due to the chronic nature of a psychiatric diagnosis, the future does not seem very bright for these patients. There is also the unlucky burden of suffering (both emotional and economic) placed on a family destined to take care of a person that will likely never become independent. These patients are forced to rely on parental and societal help, mercy and charity for decades of their painful life. Remember what Dante Alighieri wrote in *Paradise (Canto XVII, lines 58 - 60)*:

<i>Tu proverai sì come sa di sale / lo pane altrui, e come è duro calle / lo scendere e 'l salir per l'altrui scale.</i>	<i>You shall feel how salty is the taste / of another man's bread, and how hard is the way / up and down somebody else's stairs</i>
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This is true for all psychotics, particularly for people suffering from schizophrenia, since they will be incompetent and unable to perform socially for the biggest part of their life (25). The role of proxies and surrogates in decision-making is, within this frame, highly debatable. Psychotics may not be able to give their consent for starting and maintaining a pharmacological therapy even if formally requested. Meanwhile, compliance (otherwise called adherence to treatment) is measured and controlled, but some patients will have very little insight into their ailment during considerable periods of time (26).

### ***Instead of a Conclusion***

Modulating an individual's thoughts is not merely a metaphor. The set of beliefs, ideas and convictions one has grown with are integrated into one's lifestyle, and are therefore part of a unique identity forming an individual. Sub-clinical delusional experiences might be evolutionary adaptive mechanisms, and therefore not blamable (27). Navigating between antipsychiatry, denial of mental illness and futurism – while waiting for the precision medicine to integrate into the discipline of psychiatry and its therapeutic armamentarium – will help little to clarify dilemmas (28, 29).

There is also a bulk of probably insufficient data that hamper the enthusiastic views on psychopharmacology, in particular on the use of antipsychotics. We are not

merely talking about the side effect profiles: every treating clinician will ponder the risk-benefit ratio case after case. Progression is obvious and measurable, but 'miracle drugs' need to be treated with prudence and cautious skepticism. Not casually, maybe, malaria therapy of neurosyphilis for which Wagner Jauregg was granted a Nobel Prize in Medicine (the only one won from a psychiatrist), did not survive the proof of time, like many other therapies, and is actually only of historical interest (30).

Changing the mind while trying, for example, to efface delusions can very well be the consequence of a tissue remodeling (31). In this case we are talking about cerebral tissue, whose structure is moldable in a rather dramatic way, that is, through psychosurgery. More subtly, psychopharmacology seems able to do the same. Chronic exposure to antipsychotics might cause the brain to shrink or undergo other changes in size (32).

Nonetheless, there are numerous uncertainties surrounding these concerns as well, including: are these changes due to psychosis itself, and who can dispute the enormous improvements in terms of the quality of life and socialization for all psychotic patients since the discovery of antipsychotics? Very few will be able to uphold this suspicion, and not the authors of these lines, at any rate.

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